

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

29 JA 2006

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/016623

International filing date (day/month/year)
17.06.2004

Priority date (day/month/year)
29.03.2004

International Patent Classification (IPC) or both national classification and IPC
A61K38/12, A61P3/04

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/016623

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed.
 - ☒ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
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Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-9 (industrial applicability); 1-17 (partially)

because:

- ☒ the said international application, or the said claims Nos. 1-9 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-17 (partially) are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet
- ☒ the claims, or said claims Nos. 1-17 (partially) are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/016623

Box No. V Reasoned statement under Rule 43b/s.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|-------------------------------|
| Novelty (N) | Yes: Claims | 6-9, 14-17 |
| | No: Claims | 1-5, 10-13 |
| Inventive step (IS) | Yes: Claims | - |
| | No: Claims | 1-17 |
| Industrial applicability (IA) | Yes: Claims | 10-17; 1-9 see separate sheet |
| | No: Claims | - |

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/016623

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

- 1- Claims 1-9 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).
- 2- Claims 1-7, 10-15 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for the use of only 2 theoretical compound (MC4R agonist peptide "P1", MC4R agonist peptide "P2"). In the present case, the claims so lack support, and the application so lacks disclosure.
- 3- Furthermore, the examples do not specify the structure of the agonist used.

The applicant should indicate why it is believed that all the claimed, but non-exemplified possible compounds are active. It should be borne in mind that only those compounds which are suitable for solving the problem underlying the present application can be claimed (see "inventive step" below). The subject matter of a particular claim can be regarded as inventive only if all the embodiments covered provide a solution to the technical problem posed. A technical effect solving a technical problem has to be achieved by all embodiments falling within the scope of the claim. Claims covering embodiments not achieving said effect, and thus not solving the underlying technical problem, lack inventive step.

- 4- In any case, it should be noted that broad claims 1-4, 10, 11 and 12 lack novelty at least in view of D2, D3, D4, D6, D7 or D8. Documents D8 or D9 appear also to be novelty destroying for the subject matter of broad claims 5 and 13 (see below, under "novelty").
- 5- The claims as a whole lack clarity, support and disclosure (Arts. 6 and 5 PCT), and only a partial opinion with regards to the novelty, inventive step and industrial applicability is to be formulated (see below).

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

6- Reference is made to the following documents:

- D1: HASKELL-LUEVANO C ET AL: "Characterization of melanocortin NDP-MSH agonist peptide fragments at the mouse central and peripheral melanocortin receptors" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 44, no. 13, 2001, pages 2247-2252, XP002970859 ISSN: 0022-2623
- D2: PROIETTO J ET AL: "NOVEL ANTI-OBESITY DRUGS" EXPERT OPINION ON INVESTIGATIONAL DRUGS, ASHLEY PUBLICATIONS LTD., LONDON, GB, vol. 9, no. 6, June 2000 (2000-06), pages 1317-1326, XP001004696 ISSN: 1354-3784
- D3: WO 00/33658 A (HOCHGESCHWENDER UTE ; BRENNAN MILES B (US); ELEANOR ROOSEVELT INST (US) 15 June 2000 (2000-06-15)
- D4: WO 03/006604 A (MERCK & CO INC ; BEDNAREK MARIA A (US)) 23 January 2003 (2003-01-23)
- D5: HOLDER JERRY RYAN ET AL: "Structure-activity relationships of the melanocortin tetrapeptide Ac-His-DPhe-Arg-Trp-NH₂ at the mouse melanocortin receptors. 1. Modifications at the His position" JOURNAL OF MEDICINAL CHEMISTRY, vol. 45, no. 13, 20 June 2002 (2002-06-20), pages 2801-2810, XP001183565 ISSN: 0022-2623
- D6: CHEUNG ADRIAN WAI-HING ET AL: "Structure-activity relationship of linear peptide Bu-His-DPhe-Arg-Trp-Gly-NH₂ at the human melanocortin-1 and -4 receptors: Histidine substitution." BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 13, no. 1, 6 January 2003 (2003-01-06), pages 133-137, XP001183563 ISSN: 0960-894X
- D7: US 2002/143141 A1 (YAGALOFF KEITH ALAN ET AL) 3 October 2002 (2002-10-03)
- D8: WO 00/58361 A (PROCTER & GAMBLE) 5 October 2000 (2000-10-05)
- D9: WO 99/54358 A (QUADRANT HOLDINGS CAMBRIDGE ; GISPEN WILLEM HENDRIK (NL); ADAN ROGER A) 28 October 1999 (1999-10-28)

NOVELTY - Art. 33 (1) and (2) PCT

7- As indicated above, D2, D3, D4, D6, D7 or D8 all disclose the use of MC4R agonists

for treating obesity and / or for inducing weight loss. Claims 1-4, 10, 11 and 12 lack novelty therefore novelty at least in view of D2, D3, D4, D6, D7 or D8.

The MC4R agonists provided in D8 or D9 appear to fall within the structure provided in present claims 5 and 13. Hence, claims 5 and 13 appear also to be lacking novelty.

INVENTIVE STEP - Art. 33 (1) and (3) PCT

- 8- The closest prior art is represented by D8 or D9 which provide MC4R peptide agonists for the same purpose as the present application.

The closest prior art differs from the present application in that none of D7 or D8 provides the preferred agonists of the present application.

The technical effect achieved in the present application is shown in the example: continuous infusion is more effective than single daily bolus.

The objective problem posed in the present application is to provide further MC4R agonist peptides for treating metabolic disorder, inducing weight loss and / or increasing muscle mass.

The solution proposed is the use of the MC4R agonist peptides of the formula claimed in claims 6 and 14 of the present application.

- 8.1- Whereas there appears to be no explicit disclosure of such compounds in the available prior art documents, it seems that the core structure is well known and that the cyclisation of such peptides via disulfide bridges is well established. It appears that the compounds as claimed in present claims 6 and 14 are merely some of several straightforward possibilities from which the skilled man would select, without the need of inventive skill, and as a result of routine experimentation procedures, in order to solve the problem posed. No unexpected effect can be derived from the compounds provided herein.

- 8.2- Should this be denied, it should be taken into account that it seems that not all the claimed compounds would be suitable for solving the problem posed in the present application (see above). Therefore, no inventive step can be acknowledged for the subject matter of claims 1-17. A technical effect solving a technical problem has to be achieved by all embodiments falling within the scope of the claim. Claims covering embodiments not achieving said effect, and thus not solving the underlying technical problem, do not meet the requirements of Art. 33 (1) and (3) PCT, for everything falling within a valid claim has to be inventive.

INDUSTRIAL APPLICABILITY - Art. 33 (1) and (4) PCT

- 9- For the assessment of the present claims 1-9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
- 10- When / if carrying out amendments, and in order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate precisely the passages of the application as filed on which these amendments are based (also rule 66.8 (a) PCT).

Only amendments with a clearly identified basis on the application as originally filed will be taken into account for the international preliminary examination report.